the residue at any of positions 3, 4, 5, 7, 8, 9, 10, 11, 16, 21, 22, 26, 27, 30, 55, 57, 71, 75, 115, 149, 150, 151, 157, 159, 160, 163, 172, 173, 174, 176, 178, 179, 181, 183, 199, or 201 may be any naturally occurring amino acid; and

the residue at position 7 may be any naturally occurring amino acid or may be absent; or

(b) a nucleotide sequence complementary to the nucleotide sequence of (a).

Please cancel claims 36-38 and 44-46 without prejudice or disclaimer.

REMARKS

Claims 1, 2, 8, 13, 39, 40, and 42 as amended, new claim 47, and claims 3-5, 7, and 9-12 as filed are pending in the instant application. Claims 36-38 and 44-46 have been canceled without prejudice or disclaimer. Support for the amendments to the claims can be found in the specification at, for example, page 2, line 11 to page 3, line 14; page 4, lines 8-10; page 9, lines 4-7; page 13, lines 7-9; page 30, line 29 to page 31, line 6; Table I (pages 15-16); and Figures 1 and 2A-2B. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Rejections of claims 1-5, 7-13, 36, 39-43, and 46 under 35 U.S.C. § 101

The Office Action asserts a rejection of claims 1-5, 7-13, 36, 39-43, and 46, under 35 U.S.C. § 101 as lacking patentable utility. The Action states that the specification as-filed does not provide a specific, substantial, and credible utility for the claimed invention. The Action also states that Applicants' comments made in response to the Office Action mailed January 4, 2001, and the Exhibits provided by Applicants in support of these comments, are unpersuasive. It appears that the latter assertion is based primarily on the fact that the comments and Exhibits were not provided by Applicants in the as-filed specification. Applicants note that in a telephone interview with Applicants' representative Kevin Noonan on April 5, 2002, Examiner Nguyen indicated that with respect to murine FGF-like molecules, the as-filed specification did assert a specific, substantial, and credible utility.

Applicants respectfully disagree with the assertion that the comments and Exhibits provided in the response to the Office Action mailed January 4, 2001 must have been provided in the as-filed specification in order to be considered. In fact, Applicants note that under the Utility Examination Guidelines, the credibility of an asserted utility must be assessed "in view of the disclosure and *any other evidence of record (e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions." Utility Examination Guidelines, 66 Fed. Reg. 1092, (2001) (*emphasis added*); M.P.E.P. § 2107. Nevertheless, in an effort to expedite prosecution of the pending claims to allowance, Applicants have amended the claims as suggested by the Examiner to recite murine FGF-like nucleic acid molecules. Applicants' amendment of the claims to delete human FGF-like nucleic acid molecules, however, does not constitute an admission that the human FGF-like molecules lack utility or that the instant specification does not assert a specific, substantial, and credible utility for the human FGF-like molecules. Moreover, Applicants reserve the right to pursue claims directed to human FGF-like molecules in a timely filed continuation or divisional application.

As Applicants have amended the claims to recite only murine FGF-like molecules, and the Examiner has indicated that the specification asserts a specific, substantial, and credible utility for the claimed murine FGF-like molecules, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

2. Rejections of claims 1-5, 7-13, 36, 39-43, and 46 under 35 U.S.C. § 112, first paragraph

The Office Action asserts rejections of claims 1-5, 7-13, 36, 39-43, and 46, under 35 U.S.C. § 112, first paragraph, on a number of bases, which Applicants address *seriatim*.

The Action first asserts a rejection of claims 39 and 40 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Both the instant Office Action and the Office Action mailed January 4, 2001 assert that the instant specification provides neither a representative number of nucleic acid molecules falling within the scope of the genera defined by claims 39 and 40 nor

structural features common to the members of these genera to properly define the genus.

Applicants have amended claim 39 to recite an isolated nucleic acid molecule comprising a region of the nucleotide sequence of SEQ ID NO: 3, encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the polypeptide fragment has an activity of the polypeptide set forth in SEQ ID NO: 4, or is antigenic; a region of the nucleotide sequence of SEQ ID NO: 3 comprising a fragment of at least about 16 nucleotides; or a nucleotide sequence complementary to the nucleotide sequence of either of these nucleic acid molecules. Applicants contend that because claim 39, as amended, recites only fragments of the disclosed murine FGF-like nucleic acid molecule (*i.e.*, SEQ ID NO: 3), one of ordinary skill in the art could readily determine the structure of nucleic acid molecules falling within the scope of this claim. Applicants therefore respectfully request that this ground of rejection be withdrawn.

Applicants have amended claim 40 to recite an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 4 with at least one conservative amino acid substitution, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 4; a region of the nucleotide sequence of (a) comprising a fragment of at least about 16 nucleotides; or a nucleotide sequence complementary to the nucleotide sequence of either of these nucleic acid molecules. Applicants note that in the telephone interview with Applicants' representative Kevin Noonan on April 5, 2002, Examiner Nguyen indicated that claims directed to murine FGF-like variants having at least one conservative amino acid substitution would be allowable provided that Applicants indicate where in the specification support for such claims could be found. Applicants note that the instant application teaches the nucleotide sequences and corresponding amino acid sequences for murine and human FGF-like polypeptide (Figure 1 and Figures 2A-2B). The instant application also teaches that conservative amino acid substitutions may be made in those portions of the FGF-like polypeptide that are not conserved among FGF-like orthologs (page 30, line 29 to page 31, line 6). Finally, the instant application also sets forth some general rules for making conservative amino acid substitutions in Table I (pages 15-16). A sequence comparison so illustrating conserved amino acid residues in the FGF-like polypeptide sequence prepared according to the teachings of Applicants' specification is attached herein as Appendix A. In view of the teachings in the instant application, Applicants respectfully request that this ground of rejection be withdrawn.

In addition, Applicants have added new claim 47, which recites a genus of murine FGF-like molecules having at least one conservative amino acid substitution. New claim 47 is based on the amino acid sequence comparison of the murine and human FGF-like polypeptides disclosed in the instant specification (Appendix A) that indicates the structural features shared by these sequences. Applicants contend that the instant specification taught one of ordinary skill in the art to perform such a sequence comparison of the murine and human FGF-like polypeptides disclosed in the instant specification in order to determine the positions within the murine FGF-like polypeptide sequence where substitutions, either conservative or nonconservative, would be tolerated, and that such a comparison was well within the skill of one having but ordinary skill in the art.

The Office Action also asserts a rejection of claims 1-5, 7-13, 36, 39-43, and 46, under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The Office Action mailed January 1, 2001 contended that because the specification purportedly failed to disclose a specific biological function for the claimed sequences and the claimed sequences display a low sequence identity to members of the FGF family of proteins, a skilled artisan would not know how to use the claimed FGF-like nucleic acid molecules, or how to test for compounds that inhibit FGF-like polypeptide activity. The prior Office Action also contended that the specification failed to provide an enabling disclosure for using the claimed sequences to modulate the levels of a polypeptide in an animal, because the potential therapies for practicing the claimed method – e.g., antisense gene therapy – are highly unpredictable and would therefore, require undue experimentation.

As discussed in section 1 above, Applicants have amended the claims to recite only the murine FGF-like molecules. As noted in the response to the Office Action mailed January 4, 2001, the instant application discloses that, in view of the localization of FGF-like mRNA expression (primarily in the liver), the structural similarity of the FGF-like polypeptides of this invention to members of the FGF family, and the likelihood that FGF-like polypeptide is secreted into the bloodstream where it may exert effects on distal sites, the FGF-like molecules of the present invention may be useful for, *inter alia*, stimulating cells within or near the liver, regulating intestinal

cell activity, or stimulating pancreatic beta islet cells (page 5, lines 3-14). The instant application further discloses that transgenic mice expressing an FGF-like transgene of the invention exhibit an abnormal phenotype generally characterized as inhibited or delayed maturation, including reduced body weight, reduced liver weight as a percent of body weight, reduced spleen weight as percent of body weight, increased thymic weight as percent of body weight, and poorly developed ovaries with lack of significant follicular development (page 4, lines 22-28). Applicants contend that a skilled artisan would recognize that the claimed sequences could be useful, among other things, as growth or fat deposition inhibitors (page 5, lines 15-16) or in the treatment or prevention of liver-related diseases and disorders (page 5, lines 23-25). Applicants therefore contend that the instant specification teaches the skilled artisan how to use the claimed murine FGF-like nucleic acid molecules, and respectfully request that this ground of rejection be withdrawn. Applicants note that the amendment of the claims to delete human FGF-like nucleic acid molecules has been made in an effort to expedite prosecution of the pending claims to allowance, and does not constitute an admission that the instant specification does not teach the skilled artisan how to use the disclosed human FGF-like nucleic acid molecules.

Although Applicants respectfully disagree with the assertion that the specification fails to provide an enabling disclosure for using the claimed sequences to modulate the levels of a polypeptide in an animal, Applicants have canceled claims 36 and 46 to reduce the number of outstanding issues and expedite prosecution of the pending claims to allowance. Applicants reserve the right to pursue such claims in a timely filed continuation or divisional application.

3. Rejections of claims 8, 9, 12, 13, 36, 40, and 44 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claims 8, 9, 12, 13, 36, 40, and 44, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Action states that claim 39 is vague and indefinite because the claim contains an improper Markush group that recites identical elements a number of times and contains multiple dependent elements.

Applicants have amended claims 1, 39, and 40, and contend that the claims, as amended, do

not recite improper Markush groups that recite identical elements a number of times and contain

multiple dependent elements. For example, claim 1(c) now recites a nucleic acid molecule

comprising a nucleotide sequence which hybridizes under at least moderately stringent conditions to

the complement of the nucleotide sequence of either (a) or (b). Applicants contend that it is readily

apparent that claim 1(c) does not merely recite a molecule having the nucleotide sequence of claim

1(a) (i.e., the nucleotide sequence as set forth in SEQ ID NO: 3) or claim 1(b) (i.e., a nucleotide

sequence encoding the polypeptide as set forth in SEQ ID NO: 4), but rather is drawn to a molecule

having a sequence that hybridizes under at least moderately stringent conditions to the complement

of the nucleotide sequence of claim 1(a) or 1(b). Similarly, Applicants contend that it is readily

apparent that claim 1(d), which is drawn to a nucleic acid molecule comprising a nucleotide

sequence complementary to the nucleotide sequence of any of (a) - (c), does not merely recite a

molecule having the nucleotide sequence of claim 1(a), 1(b), or 1(c), but rather is drawn the

complement of the nucleotide sequence of claim 1(a), 1(b), or 1(c). Applicants contend that claims

1, 39, and 40, as amended, are no longer vague and indefinite, and therefore respectfully request that

this ground of rejection be withdrawn.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending

claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Nguyen believes it to be helpful, he is invited to contact the undersigned

representative by telephone at (312) 913-0001.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Dated: September 25, 2002

Donald L. Zuhn, Ph.D.

Reg. No. 48,710

9



AMENDMENTS TO THE CLAIMS

Marked Up Versions of Amended Claims under 37 C.F.R. 1.121(c)(1)(ii)

- 1. (Thrice Amended) An isolated nucleic acid molecule comprising a nucleotide sequence-selected from the group consisting of:
 - (a) the nucleotide sequence as set forth in SEQ-ID-NO: 1-or SEQ ID NO: 3;
- (b) a nucleotide sequence encoding the a polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4;
- (c) the nucleotide sequence of the DNA insert in ATCC Deposit No. PTA-626;
- (d)(c) a nucleotide sequence-which hybridizes under at least moderately or highly stringent conditions to the complement of any of the nucleotide sequence of either (a) (e) or (b), wherein the polypeptide encoded by the nucleic acid molecule has an activity of the polypeptide set forth in SEQ ID NO: 4; and or
- (e)(d) a nucleotide sequence complementary to the nucleotide sequence of any of (a) (c).
- 2. (Twice Amended) A recombinant host cell comprising a nucleic acid molecule comprising the nucleotide sequence of any of Claims 1, 39, or 40, or 47.
- 8. (Amended) A vector comprising the nucleic acid molecule of Claims 1, 39,-or 40, or 47.
- 13. (Twice Amended) A process for producing an protein FGF-like polypeptide comprising growing a culture of culturing the host cell of Claim 9-in under suitable-culture medium conditions to express the polypeptide, and wherein said polypeptide can be isolating isolated the protein from the culture.
- 39. (Twice Amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

- (a) a nucleotide sequence encoding a polypeptide that is at least about 80 percent identical to the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4 wherein the polypeptide has an activity of the polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4, or serves as an antigen for generating antibodies;
- (b) a nucleotide sequence encoding an allelic variant or splice variant of either the nucleotide sequence as set forth in either SEQ ID NO: 1 or SEQ ID NO: 3; the nucleotide sequence of the DNA insert in ATCC Deposit No. PTA-626; or (a) wherein the polypeptide has an activity of the polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4;
- (e)(a) a region of the nucleotide sequence of either SEQ ID NO: 1 or SEQ ID NO: 3; the DNA insert in ATCC Deposit No. PTA-626; (a); or (b); encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the polypeptide fragment has an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4, or is antigenic serves as an antigen for generating antibodies;
- (d)(b) a region of the nucleotide sequence of either SEQ ID NO: 1 or SEQ ID NO: 3; the DNA insert in ATCC Deposit No. PTA-626; or (a)—(c) comprising a fragment of at least about 16 nucleotides; or
- (e) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a) (d) and wherein the polypeptide has an activity of the polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4; and
- (f)(c) a nucleotide sequence complementary to any of the nucleotide sequence of either (a) (c) or (b).
- 40. (Twice Amended) An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:
- (a) a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4 with at least one conservative amino acid substitution, wherein the encoded polypeptide has an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4;

(b) a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4 with at least one amino acid insertion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (c) a nucleotide sequence encoding a polypeptide as set forth in either SEQ-ID-NO: 2 or SEO ID NO: 4 with at least one amino acid deletion, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (d) a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEO ID NO: 4 which has a C- and/or N- terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (e) a nucleotide sequence encoding a polypeptide as set forth in either SEQ ID NO: 2 or SEQ ID NO: 4 with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (f)(b) a region of the nucleotide sequence of any of (a) - (e) comprising a fragment of at least about 16 nucleotides; or (g) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a) - (f); and (h)(c) a nucleotide sequence complementary to any of the nucleotide sequence of either (a)—(e) or (b). A process of producing an FGF-like polypeptide comprising 42. (Amended) culturing the recombinant host cell of Claim-89 under suitable conditions to express the

polypeptide.



PENDING CLAIMS

Clean Versions of Pending Claims under 37 C.F.R. 1.121(c)(3)

- 1. An isolated nucleic acid molecule comprising a nucleotide sequence:
- (a) as set forth in SEQ ID NO: 3;
- (b) encoding a polypeptide as set forth in SEQ ID NO: 4;
- (c) which hybridizes under at least moderately stringent conditions to the complement of the nucleotide sequence of either (a) or (b), wherein the polypeptide encoded by the nucleic acid molecule has an activity of the polypeptide set forth in SEQ ID NO: 4; or
 - (d) complementary to the nucleotide sequence of any of (a) (c).
- 2. A recombinant host cell comprising a nucleic acid molecule comprising the nucleotide sequence of any of Claims 1, 39, 40, or 47.
 - 3. The recombinant host cell of Claim 2 which is a eukaryotic cell.
 - 4. The recombinant host cell of Claim 2 which is a prokaryotic cell.
- 5. A process of producing an FGF-like polypeptide comprising culturing the recombinant host cell of Claim 2 under suitable conditions to express the polypeptide.
- 7. The process of Claim 5, wherein the nucleic acid molecule comprises promoter DNA other than the promoter DNA for the native FGF-like polypeptide operatively linked to the DNA encoding the FGF-like polypeptide.
 - 8. A vector comprising the nucleic acid molecule of Claims 1, 39, 40, or 47.
 - 9. A host cell comprising the vector of Claim 8.
 - 10. The host cell of Claim 9 which is a eukaryotic cell.

- 11. The host cell of Claim 9 which is a prokaryotic cell.
- 12. A process for determining whether a compound inhibits FGF-like polypeptide activity or FGF-like polypeptide production comprising exposing a cell according to Claim 2 to the compound, and measuring FGF-like polypeptide activity or FGF-like polypeptide production in said cell.
- 13. A process for producing an FGF-like polypeptide comprising culturing the host cell of Claim 9 under suitable conditions to express the polypeptide, wherein said polypeptide can be isolated from the culture.
 - 39. An isolated nucleic acid molecule comprising:
- (a) a region of the nucleotide sequence of SEQ ID NO: 3, encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the polypeptide fragment has an activity of the polypeptide set forth in SEQ ID NO: 4, or is antigenic;
- (b) a region of the nucleotide sequence of SEQ ID NO: 3 comprising a fragment of at least about 16 nucleotides; or
- (c) a nucleotide sequence complementary to the nucleotide sequence of either (a) or (b).
 - 40. An isolated nucleic acid molecule comprising:
- (a) a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 4 with at least one conservative amino acid substitution, wherein the encoded polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 4;
- (b) a region of the nucleotide sequence of (a) comprising a fragment of at least about 16 nucleotides; or
- (c) a nucleotide sequence complementary to the nucleotide sequence of either (a) or (b).

- The process of Claim 5, further comprising recovering the polypeptide from the culture.
- 42. A process of producing an FGF-like polypeptide comprising culturing the recombinant host cell of Claim 9 under suitable conditions to express the polypeptide.
- 43. The process of Claim 42, further comprising recovering the polypeptide from the culture.
 - 47. An isolated nucleic acid molecule comprising:

wherein the residue at either position 2 or 177 may be either aspartic acid or glutamic acid; the residue at position 6 may be either threonine or serine; the residue at position 18 may be either leucine or valine;

the residue at any of positions 76, 105, or 155 may be either arginine or glutamine; the residue at either position 83 or 185 may be either glutamic acid or glutamine;

the residue at either position 99 or 158 may be either threonine or alanine;

the residue at position 146 may be either histidine or arginine;

the residue at position 154 may be either histidine or asparagine;

the residue at position 168 may be either leucine or methionine;

the residue at any of positions 3, 4, 5, 7, 8, 9, 10, 11, 16, 21, 22, 26, 27, 30, 55, 57,

71, 75, 115, 149, 150, 151, 157, 159, 160, 163, 172, 173, 174, 176, 178, 179, 181, 183, 199,

or 201 may be any naturally occurring amino acid; and

the residue at position 17 may be any naturally occurring amino acid or may be absent; or

(b) a nucleotide sequence complementary to the nucleotide sequence of (a).

4



APPENDIX A

ClustalW (v1.4) multiple sequence alignment

Alignment Score = 994 2 Sequences Aligned Conserved Identities = 159 Gaps Inserted = 1

Pairwise Alignment Mode: Slow Pairwise Alignment Parameters:

Open Gap Penalty = 5.0 Extend Gap Penalty = 0.1

Similarity Matrix: blosum

Multiple Alignment Parameters:

Extend Gap Penalty = 0.0Open Gap Penalty = 5.0

Gap Distance = 8 Delay Divergent = 40%

Similarity Matrix: blosum

Processing time: 0.4 seconds

1. hu_FGF-L vs. mu_FGF-L

Aligned Length = 210 Gaps = 1 Identities = 159 (75%) Similarities = 14 (6%)

1 MDSDETGFEHSGLWVS-VLAGLLLGACQAHPIPDSSPLLQFGGQVRQRYL 49 1 MEWMRSRVGTLGLWVRLLLAVFLLGVYQAYPIPDSSPLLQFGGQVRQRYL hu FGF-L mu_FGF-L 50 YTDDAQQTEAHLEIREDGTVGGAADQSPESLLQLKALKPGVIQILGVKTS 99 51 YTDDDQDTEAHLEIREDGTVVGAAHRSPESLLELKALKPGVIQILGVKAS 100 hu FGF-L **** * ********* *** .************ mu FGF-L hu_FGF-L 100 RFLCQRPDGALYGSLHFDPEACSFRELLLEDGYNVYQSEAHGLPLHLPGN 149 mu_FGF-L 101 RFLCQQPDGALYGSPHFDPEACSFRELLLEDGYNVYQSEAHGLPLRLPQK 150 ***** ****** ***************** hu_FGF-L 150 KSPHRDPAPRGPARFLPLPGLPPAPPEPPGILAPQPPDVGSSDPLSMVGP 199 mu_FGF-L 151 DSPNQDATSWGPVRFLPMPGLLHEPQDQAGFLPPEPPDVGSSDPLSMVEP 200

hu_FGF-L 200 SQGRSPSYAS 209 mu_FGF-L 201 LQGRSPSYAS 210 TECH CENTER 1800/300